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# Dopamine Receptor Excess and Mouse Madness

**The dopamine hypothesis of schizophrenia is based on evidence that the major antipsychotic drugs act by blocking dopamine D2 receptors and that dopamine-releasing drugs worsen symptoms. In this issue of *Neuron*, Kellendonk et al. report an elegant conditional transgenic mouse overexpressing dopamine D2 receptors selectively in the striatum. Strikingly, these animals display selective cognitive impairment typically associated with frontal cortical defects and abnormal dopamine markers in the prefrontal cortex, suggesting that striatal dopamine receptors can influence cortical dopamine function.**

The dopamine hypothesis of schizophrenia derives from a concatenation of diverse evidence (Snyder, 1976). The initial, most compelling findings were pharmacologic. In 1963, Arvid Carlsson observed changes in levels of dopamine metabolites in rats treated with antipsychotic neuroleptic drugs and speculated that these may reflect augmented firing of dopamine neurons secondary to blockade of receptors. The ability to monitor dopamine receptors by ligand binding permitted the discovery of very potent and selective blockade of dopamine D2 receptors by neuroleptic drugs with molecular potencies paralleling therapeutic potencies. Amphetamine, which releases dopamine, selectively exacerbates schizophrenic symptoms.

Patricia Goldman-Rakic (Goldman-Rakic, 1999) established a role for the dopamine neurons that project to the prefrontal cerebral cortex in regulating cognitive functions that are selectively impaired in schizophrenics. Dopamine projections to the prefrontal cortex arise from the ventral tegmental area of the midbrain. The most prominent dopamine pathway has cell bodies in the substantia nigra with axons projecting to the caudate and putamen collectively called the striatum. Degeneration of this pathway gives rise to the symptoms of Parkinson's disease so that the striatum has generally been assigned a primary role in regulating motor behavior. However, the striatum can influence the cerebral cortex via projections to the pallidum, thence to the thalamus, and onward to the cortex.

Dopamine might modulate schizophrenic behavior without being fundamental to the disease's pathophysiology. A direct link comes from studies reporting increased numbers of dopamine D2 receptors in the striatum of schizophrenic brain (Seeman and Kapur, 2000). However, prolonged treatment with neuroleptics leads to augmented numbers of D2 receptors, and there are few drug-naive schizophrenics.

If hyperactivity of dopamine systems mediated by augmented numbers of D2 receptors underlies schizophrenic dysfunction, then a transgenic mouse overexpressing D2 receptors might provide an animal model of schizophrenia. In this issue of *Neuron*, Kellendonk et al. (2006) have aimed to create such a model by creating D2 receptor transgenic mice. Most elegant about this system is that the transgene is conditional, being under the control of a tetracycline response element that can be turned off by oral administration of the antibiotic doxycycline. Additionally, the transgene is selectively expressed in the striatum and not in other areas of the brain that possess D2 receptors. The striatum of the transgenic mice displays increased numbers of D2 receptor binding sites and increased effects on adenylyl cyclase indicating that the transgenic receptors are functional. Overall behavior of the mutant mice is normal with unaltered locomotor activity, sensorimotor gating, and generalized anxiety. However, the mice display substantial defects in working memory tasks and behavioral flexibility typically associated with prefrontal cortical function. The authors provide direct evidence that the striatal D2 receptors somehow influence the cortex because the mutant mice display altered glucose metabolism, dopamine levels, and dopamine D1 receptor activation in the prefrontal cortex. Reversal of the transgene with doxycycline treatment does not reverse the cognitive defects, indicating that the behavioral deficit presumably reflects D2 receptor overexpression during fetal life.

The Kellendonk study clearly establishes an influence of striatal D2 receptors upon biochemical markers and cognitive behaviors associated with the prefrontal cortex. Do these findings teach us about the pathophysiology of schizophrenia? Do these mice provide an animal model of schizophrenia? Recent genetic studies afford a basis for optimism. Numerous workers have had some success in identifying specific genes linked to schizophrenia. Best characterized is DISC1, a cytoskeletal protein that binds to a subtype of phosphodiesterase and inhibits its catalytic activity (Millar et al., 2005). Because this phosphodiesterase metabolizes cyclic AMP, which is a second messenger for dopamine, one might speculate about some relationship. Weinberger and colleagues (Winterer and Weinberger, 2004) provided evidence that polymorphisms in catechol-O-methyltransferase (COMT) impact dopamine transmission in prefrontal cortex, prefrontal-linked cognitive behavior, and schizophrenic behavior. Thus, it is not at all farfetched to envisage dopamine disturbances eliciting schizophrenic mental aberrations. In this case, the transgenic mice developed by Kellendonk and colleagues

may provide a valuable tool for understanding this most malignant of mental disorders.

**Solomon H. Snyder**[1]
[1] Departments of Neuroscience, Pharmacology, and Psychiatry
Johns Hopkins University School of Medicine
Baltimore, Maryland 21205

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